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| 09/835,297 | 04/12/2001 | Jeffrey A. Bluestone | GNN-014CP | 4765 |
| 959 | 7590 | 09/21/2004 | EXAMINER | |
| LAHIVE & COCKFIELD, LLP. 28 STATE STREET BOSTON, MA 02109 | | | | OUSPENSKI, ILIA I |
| | | ART UNIT | | PAPER NUMBER |
| | | 1644 | | |

DATE MAILED: 09/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary**Application No.**

09/835,297

Applicant(s)

BLUESTONE ET AL.

Examiner

ILIA OUSPENSKI

Art Unit

1644

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***Period for Reply****A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.**

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 01 July 2004.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-33 is/are pending in the application.

4a) Of the above claim(s) 1-15, 32 and 33 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 16-31 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

- Certified copies of the priority documents have been received.
- Certified copies of the priority documents have been received in Application No. _____.
- Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 05/01/2002

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____

5) Notice of Informal Patent Application (PTO-152)

6) Other: _____

DETAILED ACTION

1. The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Ilia Ouspenski, Group Art Unit 1644, Technology Center 1600.

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth herein.

Upon review of the instant application, it is noted that the sequences disclosed at least on page 63 are *not accompanied by SEQ ID Numbers*. Applicant is reminded of the sequence rules which require a submission for all sequences of more than 9 nucleotides or 3 amino acids (see 37 CFR 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences which require compliance with the rules. Applicant is reminded to amend the specification and the claims accordingly.

Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) in response to this Office Action.

3. Applicant's election without traverse of Invention of Group II, (claims 16 – 17 and 22 – 26, drawn to a method of downmodulating an immune response by administering a construct comprising a portion of an antibody to CTLA4 and an MHC molecule) in the reply filed on 07/01/2004 is acknowledged. Applicant further elects the species of a syngeneic class II molecule as the MHC molecule, the species of a cellular

bilayer that is a eukaryotic cell syngeneic to the subject as the exposed surface, and the species of a phosphatidylinositol-glycan anchor as the exposed surface to which the antibody is attached. Applicant further elects the species that the immune response is against a self antigen.

Upon further consideration, and in view of the state of the art at the time the invention was made, the Examiner has determined to extend the search to the Invention of Group III, Claims 18 – 23 and 25 – 31, drawn to a method of downmodulating an immune response by causing a cell of the subject to express a portion of an antibody to CTLA4.

Thus the elected claimed invention is directed to a method of downmodulating a primary or ongoing immune response against a self antigen by administering a syngeneic cell which has exposed on its surface a syngeneic MHC class II molecule and a portion of anti-CTLA-4 antibody attached via a phosphatidylinositol-glycan anchor, or by causing a cell of the subject to express a portion of an antibody to CTLA4.

4. Claims 1 – 33 are pending.

Claims 1 – 15 and 32 - 33 are withdrawn from further consideration by the Examiner under 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 16 – 31 are under consideration in the instant application.

5. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. The provisional application 60/196,851 upon which priority is claimed appears to provide adequate support under 35 U.S.C. 112 for subject matter claimed in the instant application.

6. It is noted that the oath or declaration has not been signed by one of the named Inventors, Jeffrey A. Bluestone. It is further noted that the petition requesting that the application be accepted pursuant to 37 C.F.R. §1.47(a), filed 02/13/2002, has been granted by the Office of Petitions (mailed 05/10/2002).

7. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed*.

8. Applicant's IDS, filed 05/01/2002, is acknowledged.

9. The use of trademarks has been noted in this application at least on page 63 (e.g. Triazol Reagent). Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

In addition, Applicant is requested to review the application for embedded hyperlinks and/or other forms of browser-executable code and delete them. Embedded hyperlinks and/or other form of browser-executable code are impermissible in the text of the application as they represent an improper incorporation by reference. See MPEP § 608.01 and 608.01(p).

10. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors and spelling. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the in the specification.

Apparent errors have been noted at least on page 75, line 15, and page 76, line 10.

11. Claims 16 – 17 and 22 – 26 are objected to as being dependent on non-elected claims. Applicant is required to amend the claims to place them in independent form, to include all of the limitations of the base claim and any intervening claims.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) *the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.*

13. Claims 16 – 20 and 23 – 31 are rejected under **35 U.S.C. 102(a)** as being anticipated by Lechler et al. (WO 99/57266, of record: document A3 on IDS filed 05/01/2002; see entire document).

Lechler et al. teach and claim a method for inhibiting T-cell mediated rejection of a xenotransplanted organ by administering, or inducing expression of, a membrane associated protein which can bind to CTLA-4, such as an antibody or a single chain antibody (sFv) to CTLA-4 (see “The second aspect,” pages 4 – 6; in particular, page 4 bottom paragraph, page 5 lines 19 – 23, and page 6 first paragraph). Lechler et al. further teach that the CTLA-4 binding protein can be expressed on the surface of a cell, which preferably can also express MHC class I or II molecules on its surface (page 6 lines 1-2). Lechler et al. further teach that the MHC molecules may be those of the donor or the recipient organism, i.e. syngeneic or allogeneic (page 6 lines 25 – 26 and page 7 lines 6 – 7). The anti-CTLA-4 antibody can be attached to cell surface by transforming the cells with a vector encoding the antibody as a fusion with a transmembrane domain (page 5 lines 23 – 26).

Lechler et al. thus anticipate all species of the MHC molecules, including:

A) syngeneic class II;

- B) syngeneic class I; and
- C) allogeneic class I.

Lechler et al. further anticipate the following species of exposed surface:

- C) a cellular bilayer that is a eukaryotic cell syngeneic to the subject,
- B) a cellular bilayer that is a eukaryotic cell allogeneic to the subject

Lechler et al. also anticipate the following species of attachment of the antibody to the exposed surface:

- B) transmembrane domain.

Lechler et al. also anticipate the following species of the antigen against which the immune response is raised:

- A) against a non-self antigen.

Lechler et al. also anticipate the following species of molecule that is also expressed by the cell of the method:

- A) no MHC molecule,
- B) an MHC class I molecule, and
- C) an MHC class II molecule.

Claim 25 is included because downmodulation if the immune response mediated by CD4+ T cells is an inherent property of constructs which express MHC class II molecules. Claim 26 is included because downmodulation if the immune response mediated by CD8+ T cells is an inherent property of constructs which express MHC class I molecules.

The reference teachings thus anticipate the claimed invention.

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 16 – 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lechler et al. (of record, see entire document), in view of Linsley et al. (1999, US Patent 5,885,796; see entire document), and further in view of Chou et al. (Biotechnol. Bioeng. (1999), vol. 65, pp. 160 – 169; see entire document), and further in view of Gengoux-Sedlik et al. (1999, US Patent 5,871,747; see entire document) or, in the alternative, in view of the instant specification on page 41, first paragraph.

The claimed invention is directed to a method of downmodulating a primary or ongoing immune response against a self antigen by administering a syngeneic cell which has exposed on its surface a syngeneic MHC class II molecule and a portion of anti-CTLA-4 antibody attached via a phosphatidylinositol-glycan anchor, or by causing a cell of the subject to express a portion of an antibody to CTLA4.

Lechler et al. have been discussed supra, and teach methods of downmodulating an immune response against xenoantigens.

Lechler et al. do not specifically teach methods of downmodulating an immune response against self antigens.

Linsley et al. teach that monoclonal antibodies reactive with CTLA4 receptor can be used for treating immune system diseases mediated by T cell interactions with B7 positive cells (column 5 lines 42 – 67). Linsley et al. further teach that these diseases include autoimmune diseases, allograft rejection, graft versus host disease and chronic allergic reaction (see “Methods for using the Compositions of the Invention” in columns 16 – 20; in particular, column 17 second paragraph and column 19 third paragraph), i.e. diseases related to immune responses against both self antigens and non-self antigens.

Neither Lechler et al. nor Linsley et al. teach the attachment of the anti-CTLA-4 antibody to the cell surface via a phosphatidylinositol-glycan anchor.

Chou et al. (see entire document) teach various methods of expressing proteins in a cell so that they remain attached to the cell surface, including via a glycophosphatidylinositol lipid (GPI) anchor (see e.g. Fig. 1, lane AFP-DAF). Chou et al. discuss that GPI-anchored proteins possess potential advantages and disadvantages compared to chimeric proteins containing integral transmembrane domains (page 167 last paragraph). For example, the GPI anchor may place fewer constraints on the folding of chimeric proteins (*ibid*).

Neither of the above references teach anti-CTLA-4 antibodies exposed on an acellular surface.

Gengoux-Sedik et al. teach and claim a method of inducing an immune response in an animal by administering synthetic biocompatible microparticles carrying on their

surface one or more proteins (see entire document, in particular, claims 1 – 15 on columns 19 – 21).

Likewise, the instant specification discloses on page 41, first paragraph that microbeads comprising a surface to which antigen binding portions of an antibody and MHC molecules can be attached were known in the art at the time the invention was made.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Linsley et al., Chou et al. and Gengoux-Sedik et al. to those of Lechler et al. to obtain the claimed invention.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because the anti-CTLA-4 antibodies taught by both Lechler et al. and Linsley et al., when applied as part of membrane-bound compositions as taught by Lechler et al., would be expected to downmodulate the immune response in both transplant patients, as taught by Lechler et al. and in autoimmune diseases, as taught by Linsley et al. A skilled artisan would also be motivated to express the antibody with a GPI anchor in order to facilitate its folding on the cell surface, as taught by Chou et al., and to attach the antibodies to microbeads or microparticles, as taught by Gengoux-Sedik et al.

One of ordinary skill in the art would have been motivated to incorporate these antibodies into therapeutic constructs for treatment of autoimmune diseases, and to attach them via GPI anchors, or to the surface of microbeads, since Linsley et al. teach that such antibodies can be used for treatment of autoimmune diseases, among other conditions. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected

beneficial result would have been produced by their combination. In re Sernaker, 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. Conclusion: no claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ILIA OUSPENSKI
Examiner
Art Unit 1644

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TECH CONTROL 600

01/16/04